In Vivo Determination of the Complex Elastic Moduli of Cetacean Head Tissue

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LONG-TERM GOALS

The overall goal of this project is to determine the feasibility of *in vivo,* non-invasive measurement of the complex elastic moduli of cetacean head tissue. If this objective is met, measurement systems could be developed capable of measuring the complex elastic moduli of the head tissue of live, stranded cetaceans.

OBJECTIVES

The technical objective is to remotely generate and detect mid-frequency (1 to 10 kHz) elastic waves within the body of a living cetacean, using ultrasound and to use the measured propagation parameters of these waves to obtain the complex elastic moduli by inversion. A further technical objective is to extract tissue moduli in this manner intracranially. This objective carries considerably more technical risk since both the wave-generating ultrasound and the probe ultrasound will be attenuated, distorted and scattered by the passage through the skull.

APPROACH

The approach is to measure the complex shear and bulk modulus, from which all other moduli can be calculated. The shear modulus will be determined by measuring the speed and attenuation of shear waves generated within the tissue using focused ultrasound as a remote localized force generator. This general approach to determining the complex moduli is an application of a new medical imaging technology called elastography. The methods described by Greenleaf (Chen et al, 2002) or Fink (Fink et al, 2004) provide the basis for shear wave generation. Displacements are generated remotely in a tissue volume using two intersecting focused ultrasound beams operating at slightly different frequencies. A local "radiation force" at the focal point generates bulk and shear waves at the beat frequency of the two beams. The resulting particle displacements resulting from the passage of the shear wave can be detected remotely using a modified version of an ultrasonic Doppler vibration measurement system called NIVAMS (for Non Invasive Vibration Amplitude Measuring System) developed at Georgia Tech (see Cox and Rogers, 1987, Martin et al, 2002). The system will be

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modified to make the transmit and receive beams coaxial to permit operation in tight quarters and algorithms will be developed to enable the range at which the vibration is being measured to be determined. By measuring the amplitude and arrival time of the shear wave at two different points, the propagation speed and attenuation can be determined.

Elastic waves will be first be both remotely and directly generated in tissue phantoms and measured both remotely and directly to validate the measurement technique. The elastic properties of tissue phantoms will be obtained from remotely generated and measured data and compared with directly measured and tabulated material values. The noninvasive technique will be repeated for tissue phantoms enclosed in a simulated or hydrated real cetacean skull. Ultimately, feasibility will then be tested by seeing if valid results can be obtained from measurements on a Navy dolphin. The animal tests will be done initially for accessible tissue and subsequently for intracranial tissue. Ultrasound intensity and exposure time will be consistent with limits that have been established as safe for humans and frequencies will be kept high enough to be far above the highest frequency that is audible to the dolphin. The treatments should be harmless and painless. Propagation modeling and measurements on hydrated skulls have indicated that good focusing can be achieved through the temporal fossa and pan bone of a cetacean although the focus may not be at the intended location. By measuring bulk wave propagation along with shear wave propagation the lack of certainty as to the exact location of the focus can be overcome.

The bulk modulus will be determined extracranially using tomographic methods at ultrasonic frequencies and extrapolating to the mid-frequency range. Intracranial values will be inferred from measurements of the low frequency transfer function of the skull.

WORK COMPLETED

1. System Design The *tursiops truncatus* skull bone transmission experiments conducted in FY06 showed that ultrasound beam distortion through temporal fossa and pan bone samples was minor, and therefore the *in vivo* system would not require an adaptive focusing capability. This set the stage for a re-design of the system to a configuration with significantly reduced complexity and cost.

2. Transducer Design and Purchase The revised system design features a novel arrangement of a pair of dual element confocal transducers, These transducers were specced , a suitable fabricator/vendor was identified and the transducers were purchased, tested and found to conform to the specifications.

3. Range Resolving NIVAMS The measurement system requires a NIVAMS which can measure the motion of tissue located within specified range bins. An approach to building such a system has been devised and shown to be feasible.

4. Animal Use Protocol The animal use protocol was rewritten to account for changes to the system design and measurement approach, as well as an assessment that there were no suitable animal models for simulating the extracranial tissue and skull structure of any cetacean. The new protocol was developed with the assistance of Drs. Sam Ridgway and Jim Finneran. In-vivo measurements on *tursiops truncatus* will be made at SPAWAR (San Diego) following system testing on tissue-mimicking phantoms.

RESULTS

System design: The revised system design features a novel arrangement of a pair of dual element confocal transducers, as shown in Figure 1. The radiation force generation (RFG) transducer contains two spherically focused ceramic rings operating with a center frequency of 2.5 MHz. The two rings of the radiation force generation (RFG) transducer are driven at two different frequencies, f and $f+\Delta f$, both near 2.5 MHz. At the focal region of the transducer, the combination of the two frequencies results in modulation of the focal volume at a frequency Δf, which is the frequency at which shear properties will be evaluated. Radiation force arising from the confocal field generates both bulk and shear waves, with the latter preferentially excited because the corresponding wave admittances in the tissues of interest are expected to be orders of magnitude larger.

The propagation of shear and bulk waves will be observed using a second dual ring dual ring confocal transducer the NIVAMS measurement System (NMS). One ring of the NMS transducer will be used as a source, ensonifying the tissue at approximately 1.3 MHz. The field scattered by the tissue will be measured by the second ring of the NMS transducer. The received data will contain Doppler sidelobes imparted by the propagation of elastic waves at the modulation frequency Δf of the RFG transducer, and will be analyzed to produce the magnitude and phase of vibration at each measurement point

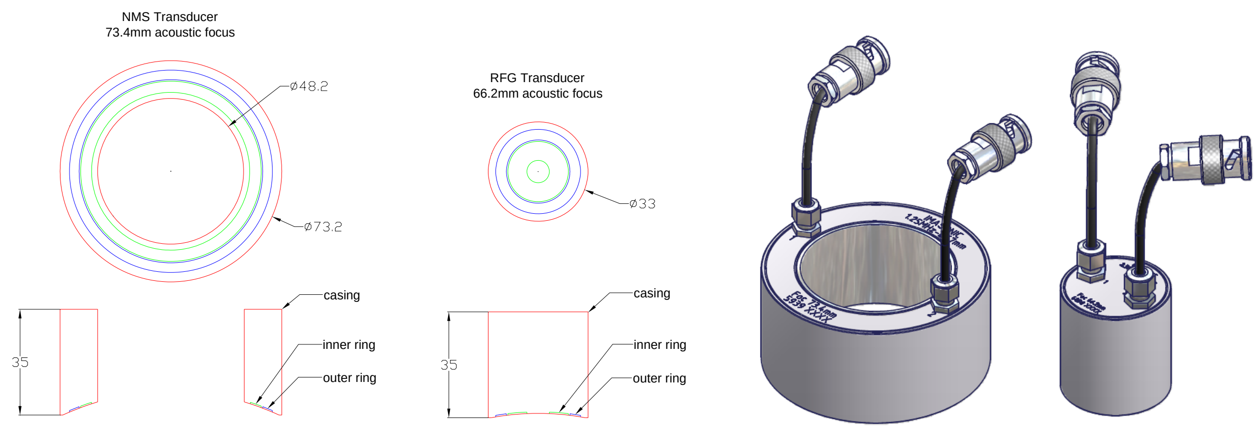

Figure 1: Transducer designs
Left: Drawings (Dimensions in mm) Right: Sketch

Both rings of both transducers were designed to focus at a tissue depth of approximately 2.5 inches, based upon review of extracranial *tursiops* tissues images and a fairly large focal depth. The NMS and RFG elements are designed so that when placed on the skin surface, both transducers have the same effective focal point. Most measurements will be made with the transducers in direct contact with the skin of the animal. However, since the transducers have fixed focal lengths, imaging of motions in tissues within approximately 1.5" of the skin surface will require standing off the transducers from the skin.

The procedures for making a shear wave speed measurement for a single anatomical location were refined as follows. The RFG transducer is placed within the NMS transducer, as in Figure 2, with both in contact with the skin. Ultrasonic gel will be used to provide acoustic coupling. Three co-linear spatial measurement points are needed to estimate the speed, attenuation and local spreading along the propagation path. These points will be acquired by changing the relative positions of the RFG and NMS transducers over a short distance (<15mm). For each measurement location, a sequence of tests will be run to cover the frequency range of interest in a modest number of steps. For a given fixed anatomical measurement location, measurements will be made at a minimum of six transducer relative positions in order to estimate the desired quantities in two orthogonal directions. Additional locations may be necessary pending (real time) analysis of measurement signal to noise ratio.

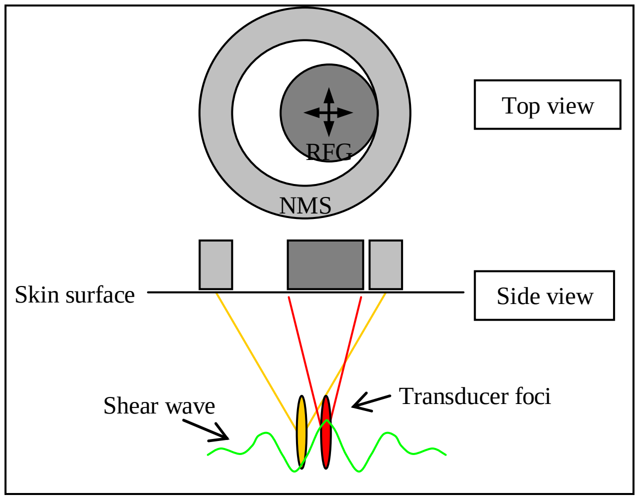

Figure 2: Measurement Configuration

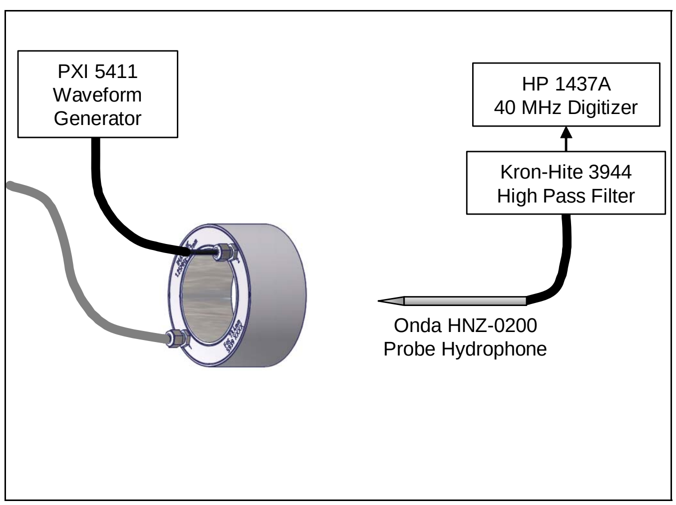

Figure 3: Calibration setup showing transducer and probe hydrophone

After designing the transducers, Georgia Tech consulted with several transducer manufacturers, ultimately contracting with Imasonic Inc (France) to build one each of the RFG and NMS. A sketch of final designs is shown in on the right hand side of Figure 1. The casings are waterproof, and the actual cable lengths are 10 feet. Delivery took approximately twenty weeks. Upon receipt of the transducers, they were calibrated in a 35 gallon tank filled with tap water. The measurements were made with the instrumentation shown in Figure 3. The needle probe hydrophone was attached to a

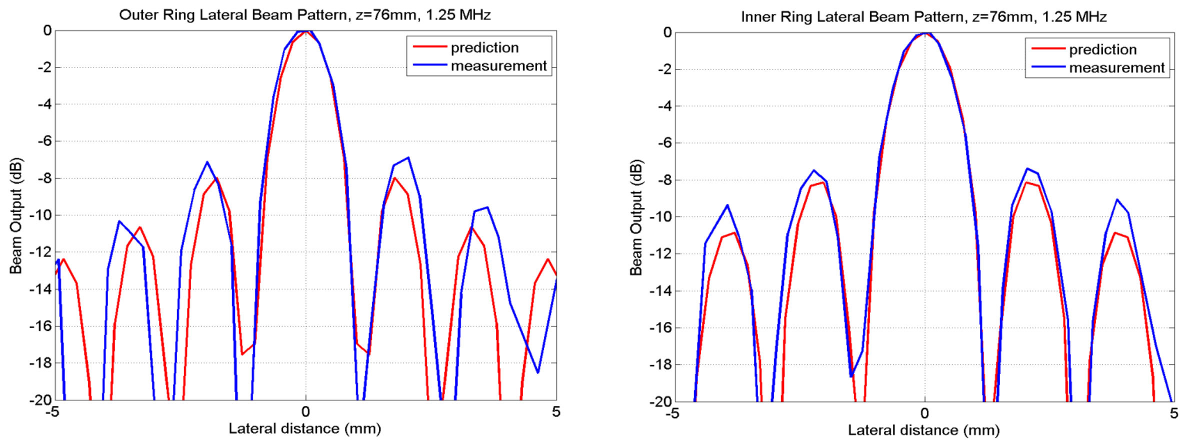

Figure 4: NMS transducer lateral beam pattern

positioner, with expected positional accuracy of approximately +/- 0.1mm. Both the axial and lateral beam patterns were measured, with the former measured at 76mm from the plane of the outer casing edge. An example result is shown for the NMS transducer in Figure 4. The measured beam pattern (pressure field normalized by the value at x=0 (on-axis) is compared with a numerical prediction for ring transducer output at 76mm (just beyond the acoustic focus), ignoring the casing, outer matching layer, and other manufacturing aspects. The predicted and measured main lobe beamwidths are nearly identical. The measured sidelobe levels tend to be 10-20% higher than predicted, although the cause is not currently known. *The significance of these results is that the spatial field distributions are largely as expected, and that the deviations will not limit system performance*.

Range resolving NIVAMS There are two technical issues that need to be addressed in order to develop an ultrasonic vibrometer that is suitable for the non-invasive / non-intrusive measurement of cetacean tissue. These are achieving an acceptable signal-to-noise ratio (SNR) in the vibration measurements and achieving an acceptable spatial resolution for those measurements in the area of the vibrating tissue. There is a fairly complex set of tradeoffs among these issues.

Ultrasonic vibrometers work by inferring the vibrational displacement of a surface from the modulation of an ultrasonic signal that is reflected from it. In order to measure vibrations with amplitudes on the order of 1nm using an ultrasonic interrogation signals in the range of 1 MHz, it is necessary to know what the unmodulated reflection from the surface would have been to an accuracy of 1 part in 100,000 (100 dB). This is a much more stringent requirement than that encountered with commercial laser-Doppler vibrometers (LDVs) because optical wavelengths are considerably shorter than practical acoustic wavelengths. In their original work with ultrasound, Cox and Rogers (1987) achieved the necessary dynamic range by using a spectrally pure interrogation signal where the energy that would have been reflected in nearby sidebands (±1 kHz) by a stationary surface could be assumed to be zero. This was also the strategy that was later employed by Martin et al (2002, 2004) and by Finneran and Hastings (2004) when the technique was expanded to include measurements of vibrational phase and real-time measurement of transient vibrations. In all of this work the central issue was transmitting and measuring an ultrasonic signal with sufficient spectral purity. For the current application, this is an impractical strategy because it precludes resolving the vibrating surface in range but instead provides a depth-integrated output that would difficult to interpret in a complex environment such as the interior of a cetacean skull.

Target ranging is generally accomplished in sonar systems by transmitting a pulse signal and separating the received echoes in the time domain. The ability to distinguish a particular target from others in its vicinity depends on the duration of the pulse signal, which is directly related to its bandwidth. Shorter duration pulses that facilitate the discrimination of more targets over a given range require more bandwidth than do longer pulses. In fact though, it is the bandwidth and not the duration of the transmitted signal that is its salient feature, because pulse compression can be used to synthesize the response of the system to any signal with identical bandwidth to the one with which it has been interrogated. Several schemes were considered for using an ultrasonic signal with large bandwidth to measure vibrations and resolve the range of the vibrating surface. The scheme that was deemed to offer the best combination of range resolution and SNR for the vibration measurement is one where the transmitted signal is composed of a sum of evenly incremented discrete frequency components each with a high degree of spectral purity. The received signal will be digitized and pulse compressed so that each range of interest can by windowed in the synthesized time domain. The result of this manipulation preserves the spectral purity of each transmitted component and allows the vibration at each range of interest to be inferred using previously established techniques. The primary hurdles in implementing this scheme were producing an appropriate time-domain driving signal and preserving the information which it contained in a subsequent analog to digital conversion. Ideally, the optimal signal can be represented as a sum of sinusoids with spacing comparable to the inverse of the total reverberation time that is observed in pulsed transmitted and received signal and phases that are randomized in order to minimize the crest factor of the transmitted signal. The total number of individual spectral components is proportional to the number of separable echos that can be analyzed within that reverberation time. Figure 5 shows an example of a transmit signal with 80 spectral lines intended to examine a field with a 64 μS reverberation time (16 kHz spacing). Figure 6 shows a portion of a simulation of the pulse-compressed received signal returned from five different vibrating objects within the field. Each of these pulses can be processed separately to determine the vibration of the scattered. Figure 7 shows a portion of the spectrum around a single tone in the transmitted signal.

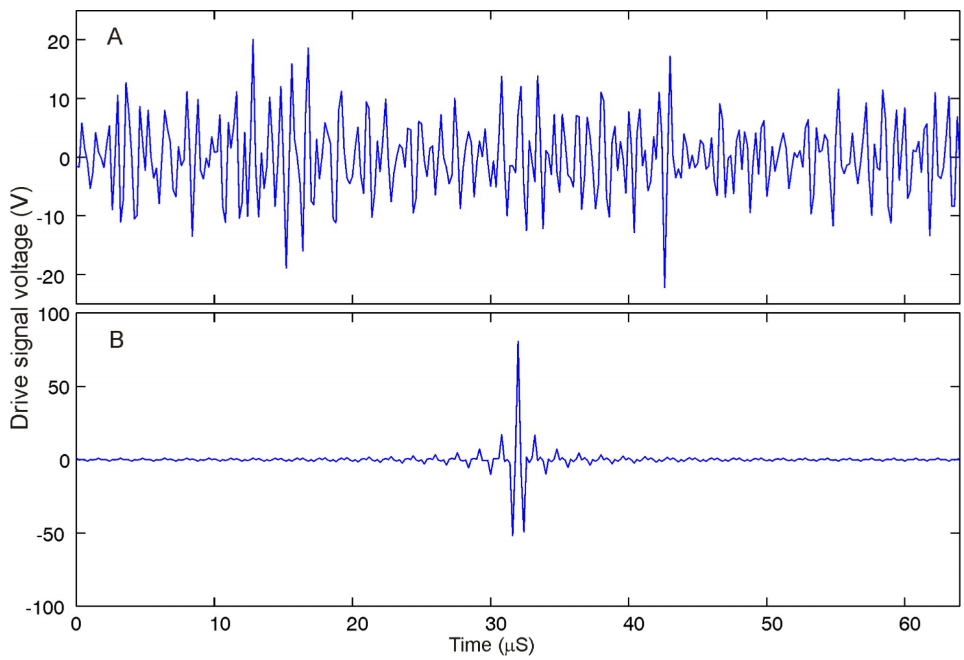

Figure 5: Uncompressed (A) and compressed (B) signals with identical spectra: 80 discrete tones spanning 625 KHz to 1.875 MHz. One cycle is shown, the actual signals are continuous with a 64 μs periodicity.

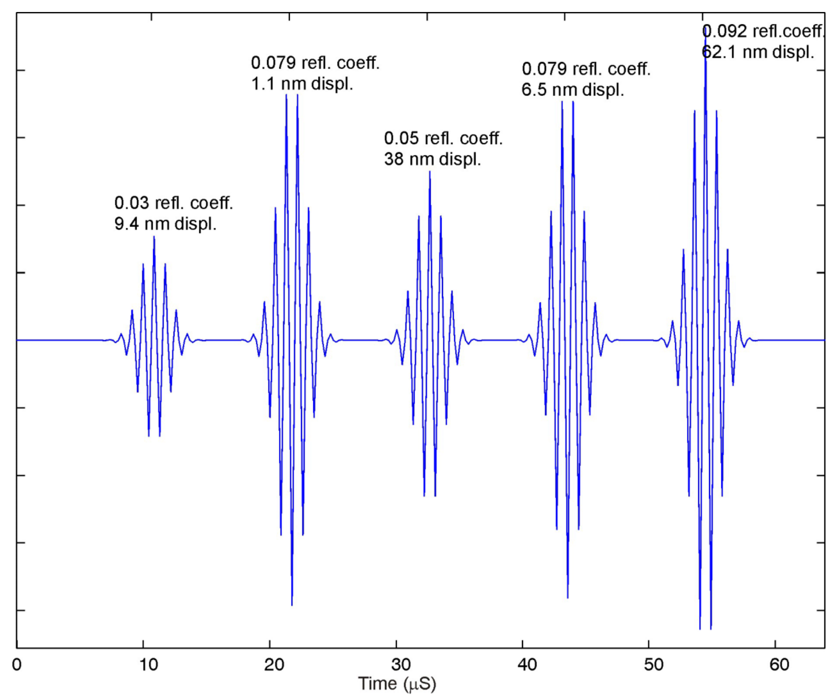

Figure 6: Pulse compressed echoes from 5 separate reflectors interrogated with the signal depicted in Figure 5A, the reflection coefficient and the magnitude of 1kHz CW vibration corresponding to each of the reflectors is indicated on the figure

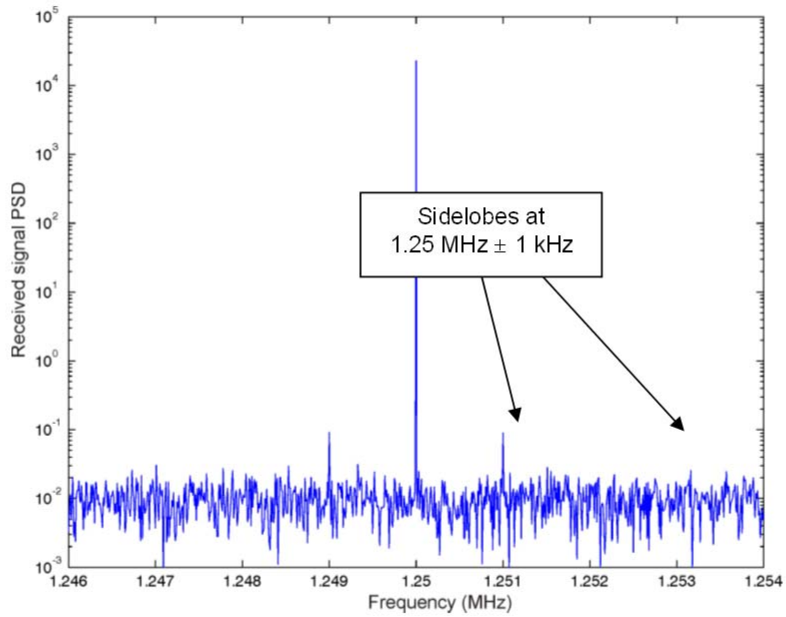

Figure 7: Spectrum of the 1.25 MHz tone (+/- 4 kHz) of a drive signal reflected from a surface vibrating at 1 KHz with an amplitude of 1 nm in the presence of simulated noise

Minimizing clock jitter and bit resolution errors: Errors are introduced into both the transmitted signal and the digital representation of the received signal from which the vibration is extracted as a result of the non-ideal behavior of digitizers. In order to perform the required demodulation of the received signal it is necessary to synchronize the clocking of the analog to digital conversion (ADC) of that signal with the transmitted ultrasonic carrier. Simply setting a common rate for both devices is far from sufficient to accomplish this because a mismatch as small as 1 part in 1 billion (1MHz ± 1mHz) would introduce the dominant error source into the measurements. Similarly, random jitter in the common clock introduces broadband noise into the measurement by broadening both the actual bandwidth of the transmitted signal and the apparent bandwidth of the received signal. Clock jitter at some level is unavoidable. Under otherwise ideal circumstances, this will introduce the self-noise limit of the sensor. In order to minimize the effects of both jitter and clock-mismatch, an SRS CG635 clock generator has been integrated into the system. This has very low clock jitter (-130 dBc/Hz at 10MHz±1kHz) and provides a common clock for both the transmitted and received signals. The other error source which is intrinsic in ADC is the bit resolution of the digitizer which rounds each sample of the input to the nearest amplitude bin. This proved to be a problem that could be resolved with existing hardware for the ADC by using a National Instruments NI-5911 digitizer with 14-bit resolution at a 5MHz sampling rate. Both jitter and bit resolution proved to be more difficult problems to address in signal generation. In order to achieve the required bandwidth in a cost effective way (using an array of synchronized oscillators was an obvious but very expensive alternative) required a programmable waveform generator. However, clocking all of the existing units quickly enough to produce the desired transmit signals resulted in excessive noise. As an alternative to this, it was decided to generate the signal's bandwidth at low frequency using a programmable generator and to mix this with an ultrasonic carrier frequency in an analog mixer to produce the appropriate bandwidth. At low frequencies, programmable generators provide cleaner outputs because jitter noise is a function of both clock jitter and the frequency of generation. The overall configuration of this system can be seen in Figure 8. The spectrum of the measured receive signal is shown in Figures 9 (full bandwidth) and 10 (partial bandwidth). The horizontal lines in Figure 10 indicate two additional SNR improvements that are not apparent from the figure. The first of these is the gain that could be achieved if the onboard memory of the digitizer were expanded to permit a one-second record length. The second indicates the improvement achieved by integrating the results of all of the spectral lines in the signal in comparison to the signal line which is depicted.

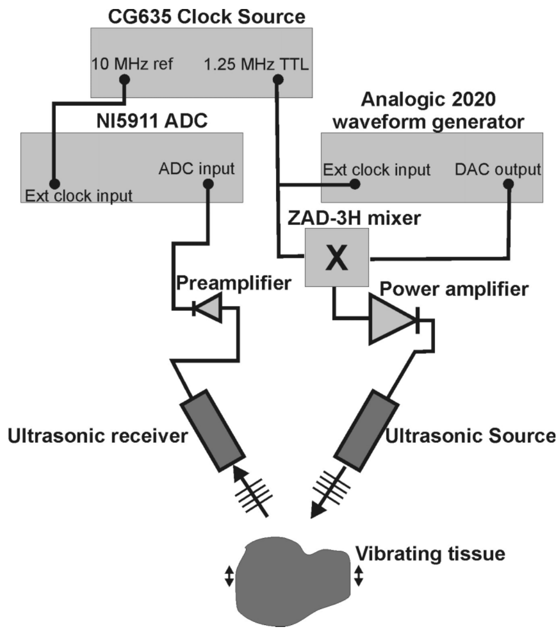

Figure 8: layout of vibrometer components sharing a common clock

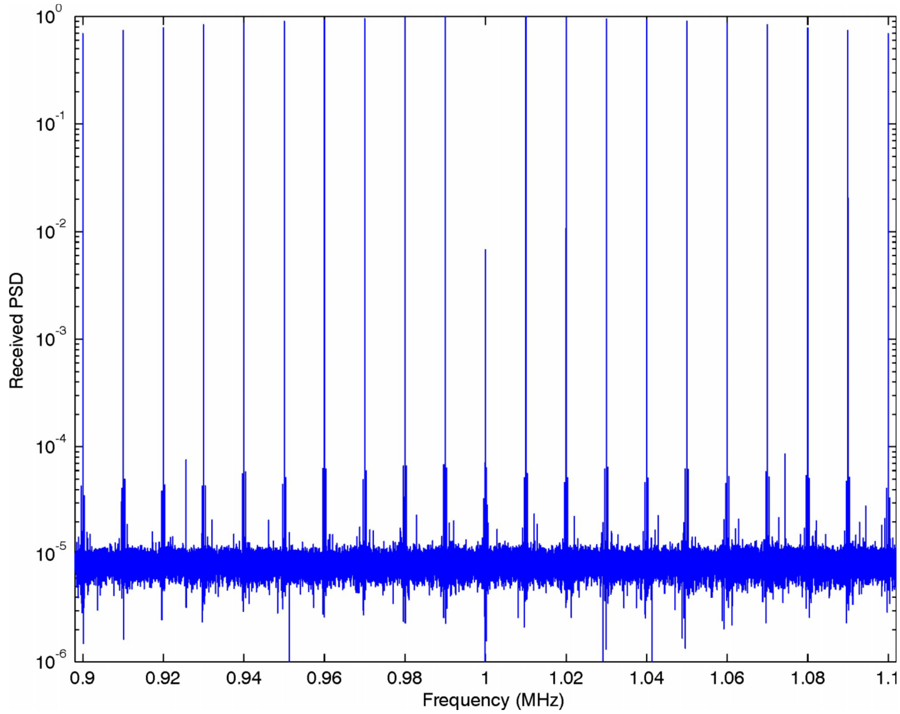

Figure 9: Measured spectrum of a signal comprised of 20 discrete tones spanning from 900 kHz to 1.1 MHz in 10 kHz steps

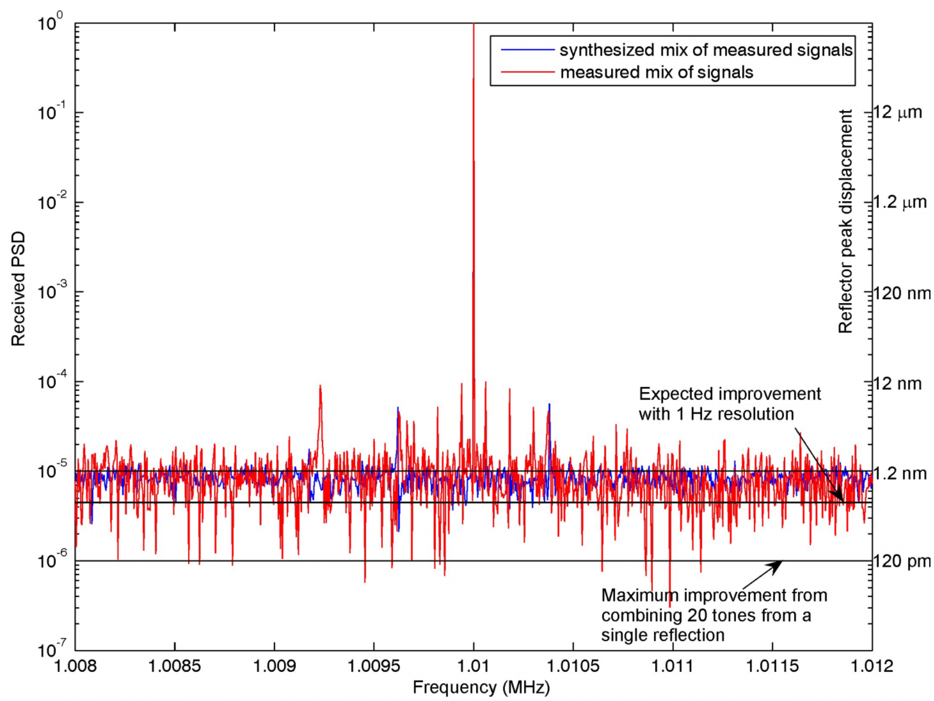

Figure 10: Measured spectrum around the 1.01 MHz line of the signal shown in figure 5. Black lines indicate effective noise floors under other measurement scenarios which offer a potential for 20 dB SNR improvement

IMPACT/APPLICATIONS

There is considerable interest in the development of structural acoustic models for the cetacean head for two main reasons: 1) to better understand biomechanics of sound reception and production in cetaceans, and 2) to understand and hopefully mitigate any harmful effects of man-made sound on their health and behavior. The development and validity of these models is severely limited by an almost complete lack of knowledge of the mechanical properties of the constituent tissue. The models can be no better than the material parameters which are provided to them. It is known that these properties change upon the death of the animal. There is thus considerable interest in being able to measure these properties *in vivo*. The techniques and instrumentation investigated here should also have biomedical application.

RELATED PROJECTS

None

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